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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	**10/006,063**
Filing Date	**December 6, 2001**
First Named Inventor	**Kevin P. Baker**
Group/Art Unit	**1647**
Examiner Name	**Fozia M. Hamud**
Total Number of Pages in This Submission: **122**	**Attorney Docket Number**	**39780-2830 P1C3**

ENCLOSURES *(check all that apply)*

- ☒ **Fee Transmittal Form**
  - ☐ Fee Attached
- ☐ Amendment/Response
  - ☐ After Final
  - ☐ Version With Markings Showing Changes
  - ☐ Affidavits/declaration(s)
- ☒ **Extension of Time Request**
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
  - ☐ Copy of Notice
- ☐ Copy of an Assignment
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, by Assignee to Exclusion of Inventor Under 37 C.F.R. §3.71 With Revocation of Prior Powers
- ☐ Terminal Disclaimer
- ☐ Small Entity Statement
- ☐ Request for Refund
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ **Appeal Communication to Group** ***(Appeal Notice, Brief, Reply Brief)***
- ☐ Proprietary Information
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Firm or Individual name	**HELLER EHRMAN LLP**	**BARRIE D. GREENE (Reg. No. 46,740)**	
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Date	**JULY 27, 2005**	Customer Number:	**35489**

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FEE TRANSMITTAL for FY 2005

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) **1,520.00**

Complete if Known	
Application Number	10/006,063
Filing Date	December 6, 2001
First Named Inventor	Kevin P. Baker
Examiner Name	Fozia M. Hamud
Art Unit	1647
Attorney Docket No.	39780-2830 P1C3

METHOD OF PAYMENT *(check all that apply)*

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Deposit Account Number: **08-1641(39780-2830P1C3)**

Deposit Account Name: **HELLER EHRMAN, LLP**

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	300	2001	150	Utility filing fee	
1002	200	2002	100	Design filing fee	
1003	200	2003	100	Plant filing fee	
1004	300	2004	150	Reissue filing fee	
1005	200	2005	100	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =		X		=
Independent Claims		- 3** =		X		=
Multiple Dependent						=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	50	2202	25	Claims in excess of 20
1201	200	2201	100	Independent claims in excess of 3
1203	360	2203	180	Multiple dependent claim, if not paid
1204	200	2204	100	** Reissue independent claims over original patent
1205	50	2205	25	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	120	2251	60	Extension for reply within first month	
1252	450	2252	225	Extension for reply within second month	
1253	1,020	2253	510	Extension for reply within third month	1020.00
1254	1,590	2254	795	Extension for reply within fourth month	
1255	2,160	2255	1,080	Extension for reply within fifth month	
1401	500	2401	250	Notice of Appeal	
1402	500	2402	250	Filing a brief in support of an appeal	500.00
1403	1,000	2403	500	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	500	2452	250	Petition to revive - unavoidable	
1453	1,500	2453	750	Petition to revive - unintentional	
1501	1,400	2501	700	Utility issue fee (or reissue)	
1502	800	2502	400	Design issue fee	
1503	1,100	2503	550	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	790	2809	395	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	790	2810	395	For each additional invention to be examined (37 CFR 1.129(b))	
1801	790	2801	395	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

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SUBMITTED BY

(Complete *(if applicable)*)

Name *(Print/Type)*	Barrie D. Greene	Registration No. *(Attorney/Agent)*	46,740	Telephone	(650) 324-7000
Signature	*Barrie Greene*			Date	July 27, 2005

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: Hamud, Fozia M.
Kevin P. BAKER, et al.	Art Unit: 1647
Application Serial No. 10/006,063	Confirmation No: 8559
Filed: December 6, 2001	Attorney's Docket No. 39780-2830 P1C3
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	**Customer No. 35489**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANTS' BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On November 29, 2004, the Examiner made a final rejection to pending Claims 28-36 and 38-40. A Notice of Appeal was filed on February 28, 2005.

Appellants hereby appeal to the Board of Patent Appeals and Interferences from the last decision of the Examiner. A request for a 3 month extension of time is filed concurrently herewith.

The following constitutes Appellants' Brief on Appeal.

08/01/2005 ZJUHAR1 00000001 081641 10006063
01 FC:1402 500.00 DA

08/01/2005 ZJUHAR1 00000001 081641 10006063
02 FC:1253 1020.00 DA

1. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the patent application U.S. Serial No. 09/946,374 recorded January 8, 2002, at Reel 012288 and Frame 0504.

2. RELATED APPEALS AND INTERFERENCES

The claims pending in the current application are directed to a polypeptide referred to herein as "PRO1293". There exist two related patent applications, (1) U.S. Serial No. 10/015,869, filed December 11, 2001 (containing claims directed to polynucleotides encoding PRO1293 polypeptides), and (2) U.S. Serial No. 10/006,818, filed December 6, 2001 (containing claims directed to antibodies that bind PRO1293 polypeptides). The 10/015,869 application is still pending. The 10/006,818 application is also under final rejection from the same Examiner and based upon the same outstanding rejection, and appeal of this final rejection is being pursued independently and concurrently herewith.

3. STATUS OF CLAIMS

Claims 28-36 and 38-40 are in this application.

Claims 1-27 and 37 are canceled.

Claims 28-36 and 38-40 stand rejected and Appellants appeal the rejection of these claims.

A copy of the rejected claims involved in the present Appeal is provided as Appendix A.

4. STATUS OF AMENDMENTS

There were no amendments to the claims submitted after final rejection. All previous amendments to the claims have been entered.

5. SUMMARY OF THE INVENTION

The invention claimed in the present application is related to an isolated polypeptide comprising the amino acid sequence of the polypeptide of SEQ ID NO:77; the amino acid

sequence of the polypeptide-of SEQ ID NO:77, lacking its associated signal peptide; the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:77; or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203292 (Claims 33-36 and 38). The invention is further directed to polypeptides having at least 80%, 85%, 90%, 95%, or 99% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO:77; the amino acid sequence of the polypeptide-of SEQ ID NO:77, lacking its associated signal peptide; the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:77; or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203292, wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumor (Claims 28-32). The invention is further directed to a chimeric polypeptide comprising one of the above polypeptides fused to a heterologous polypeptide (Claim 39), and to a chimeric polypeptide wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin (Claim 40).

The full-length PRO1293 polypeptide having the amino acid sequence of SEQ ID NO:77 is described in the specification at, for example, page 8, lines 2-13, page 338, lines 1-5, Example 26, in Figure 46 and in SEQ ID NO:77. The cDNA nucleic acid encoding PRO1293 is described in the specification at, for example, Example 26, in Figure 45 and in SEQ ID NO:76. Page 287, lines 20-24 of the specification provides the description for Figures 45 and 46. PRO polypeptide variants having at least about 80% amino acid sequence identity with a full length PRO polypeptide sequence, a PRO polypeptide sequence lacking the signal peptide, or an extracellular domain of a PRO polypeptide are described in the specification at, for example, page 302, lines 4-26. The preparation of chimeric PRO polypeptides, including those wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin, is set forth in the specification at page 358, lines 11-34. Examples 128-131 describe the expression of PRO polypeptides in various host cells, including *E. coli*, mammalian cells, yeast and Baculovirus-infected insect cells. PRO1293 is described as having amino acid sequence identity with the human Ig heavy chain V region protein and as being a newly identified member of the Ig superfamily of proteins (see, for example, page 338, lines 1-5). Finally, Example 143, in the

specification at page 494, line 20, to page 508, line 28, sets forth a Gene Amplification assay which shows that the PRO1293 gene is amplified in the genome of certain human lung and colon cancers (see page 507, lines 5-12, and Table 8).

6. ISSUES BEFORE THE BOARD

I. Whether Claims 28-36 and 38-40 satisfy the utility requirement of 35 USC §101.

II. Whether Claims 28-36 and 38-40 satisfy the enablement requirement of 35 USC §112, first paragraph.

III. Whether Claims 28-32 satisfy the written description requirement of 35 USC §112, first paragraph.

IV. Whether Claims 28-36 and 38-40 are patentable under 35 U.S.C. §102(a) over Botstein *et al.*, WO200053751 and Baker *et al.*, WO200012708.

7. GROUPING OF CLAIMS

With respect to Issue I, all claims (Claims 28-36 and 38-40) stand and fall together.

With respect to Issue II, all claims (Claims 28-36 and 38-40) stand and fall together.

Issue III concerns only Claims 28-32, which claims stand and fall together.

With respect to Issue IV, all claims (Claims 28-36 and 38-40) stand and fall together.

8. ARGUMENTS

Summary of the Arguments:

Issue I: Utility

Claims 28-36 and 38-40 stand rejected under 35 U.S.C. §101 as allegedly lacking either a specific and substantial asserted utility or a well established utility. Appellants have previously explained that patentable utility of the PRO1293 polypeptides is based upon the gene amplification data for the gene encoding the PRO1293 polypeptide. The specification discloses that the gene encoding PRO1293 showed significant amplification, ranging from 2.2 to 5 fold, in 3 different lung and colon tumors. Appellants have also submitted, with their Response filed

September 9, 2004, the Declaration of Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

The Examiner has asserted that "the instant specification does not demonstrate that the increased copy number of PRO1293 in lung and colon tumors leads to an increased expression of PRO1293 in these tumors." (Page 4 of the Office Action mailed November 29, 2004). In support of this assertion, the Examiner has cited a reference by Hu *et al.* as evidence that "gene amplification does not *necessarily* result in increased expression at the mRNA and polypeptide levels" (Page 4 of the Office Action mailed November 29, 2004; emphasis added). The Examiner has further cited Pennica *et al.* in support of the assertion that "protein levels cannot be accurately predicted from the level of the corresponding gene." (Page 5 of the Office Action mailed May 13, 2004).

Appellants submit that the Examiner applied an improper legal standard when making this rejection. The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant.

The two sole references cited by the Examiner do not suffice to make a *prima facie* case that more likely than not no generalized correlation exists between gene (DNA) amplification and increased polypeptide levels. In particular, the teachings of Pennica *et al.* are not directed towards genes in general but to genes within a single family and thus, these teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels. Nor does Hu *et al.* suffice to show that a lack of correlation between gene amplification data and the biological significance of cancer genes is typical.

In contrast, Appellants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an

elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in Appellants' Response filed September 9, 2004) collectively teach that in general, gene amplification increases mRNA expression. Second, the Declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels. Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (i.e., that it is more likely than not informative of the protein level).

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA, and polypeptide levels, these instances are exceptions rather than the rule. In the majority of amplified genes, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1293 gene, that the PRO1293 polypeptide is concomitantly overexpressed. Thus, the claimed PRO1293 polypeptides have utility in the diagnosis of cancer.

Appellants further submit that even if there is no correlation between gene amplification and increased mRNA/protein expression, (which Appellants expressly do not concede), a polypeptide encoded by a gene that is amplified in cancer would **still** have a specific, substantial, and credible utility. Appellants submit that, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin (submitted with Appellants' Response filed September 9, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor as demonstrated by the real-world example of the breast cancer marker HER-2/neu.

Accordingly, Appellants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed PRO1293 polypeptides.

Issue II: Enablement

Claims 28-36 and 38-40 stand rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Page 4 of the Office Action mailed November 29, 2004). Claims 28-32 further stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement for the claimed polypeptide variants.

Appellants submit that, as discussed above, the PRO1293 polypeptides have utility in the diagnosis of cancer. Based on such a utility, one of skill in the art would know exactly how to use the claimed polypeptides for diagnosis of cancer, without any undue experimentation.

Appellants note that the claimed variants, in addition to having at least 80% amino acid sequence identity to SEQ ID NO:77, also have the functional limitation that "the nucleic acid encoding said polypeptide is amplified in lung or colon tumors." Thus the claimed variants all share the disclosed utility of the PRO1293 polypeptide in the diagnosis of cancer. The specification provides ample guidance to allow the skilled artisan to identify those polypeptide variants which meet the limitations of the claims, including a detailed protocol for the gene amplification assay. The specification also provides detailed guidance as to how to identify and make polypeptides having at least 80% amino acid sequence identity to PRO1293 (SEQ ID NO:77). Accordingly, one of ordinary skill in the art would understand how to make and use the recited polypeptide variants without any undue experimentation.

Issue III: Written Description

Claims 28-32 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking adequate written description for the claimed variant polypeptides. In particular, the Examiner has asserted that "the claims are not defined by structure and functional identity." (Page 12 of the Office Action mailed November 29, 2004).

Appellants note that the claims recite structural features, namely, 80% sequence identity to SEQ ID NO:77, which are common to the genus. The specification provides detailed guidance as to how to identify the recited variants of SEQ ID NO:77, including methods for determining percent identity between two amino acid sequences, as well as listings of exemplary and preferred sequence substitutions. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids, namely, that the encoding nucleic acid is amplified in lung and colon tumors. Example 143 of the present application provides step-by-step guidelines and protocols for a gene amplification assay. By following the disclosure in the specification, one skilled in the art can easily test whether a gene encoding a variant PRO1293 protein is amplified in lung or colon tumors. Accordingly, one of skill in the art could identify whether the variant PRO1293 sequence falls within the parameters of the claimed invention.

Accordingly, a description of the claimed genus has been achieved by the recitation of both structural and functional characteristics.

Issue IV: Anticipation by Botstein *et al.*, WO 2000053751 and/or Baker *et al.*, WO 200012708

Claims 28-36 and 38-40 stand rejected under 35 U.S.C. §102(a) as being anticipated by Botstein *et al.*, WO 2000053751, published on September 14, 2000, and by Baker *et al.*, WO 200012708, published on March 9, 2000.

The instant application claims priority to U.S. Provisional Application Serial No. 60/162,506, filed on October 29, 1999, over ten months before the publication date of Botstein *et al.* and over four months before the publication date of Baker *et al.* The instant application has not been granted the earlier priority date on the grounds that "the parent application does not teach how to use the claimed invention in a manner that satisfies the requirements under 35 U.S.C. 112, first paragraph." (Page 13 of the Office Action mailed November 29, 2004). Appellants respectfully submit that as discussed above under Issues I and II, the presently claimed invention is supported by a specific, substantial and credible utility and, therefore, the present specification teaches one of ordinary skill in the art "how to use" the claimed invention

without undue experimentation. Accordingly, the instant application is entitled to the effective filing date of October 29, 1999, and thus neither Botstein *et al.* nor Baker *et al.* is prior art.

These arguments are all discussed in further detail below under the appropriate headings.

ISSUE I: Claims 28-36 and 38-40 satisfy the utility requirement of 35 USC §101

Claims 28-36 and 38-40 stand rejected under 35 U.S.C. §101 because allegedly "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." (Page 3 of the Office Action mailed November 29, 2004).

Appellants submit, for the reasons set forth below, that the specification discloses at least one credible, substantial and specific asserted utility for the claimed PRO1293 polypeptides.

A. The Legal Standard for Utility

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler*[4] the CCPA acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka*[6] the CAFC reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden to prove that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11], [12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the

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[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*.

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

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[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B)(1).

B. **Proper Application of the Legal Standard**

Appellants respectfully submit that Appellants rely on the gene amplification data for patentable utility of the claimed PRO1293 polypeptides, and that the gene amplification data for the gene encoding the PRO1293 polypeptide is clearly disclosed in the instant specification under Example 143.

It was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 143 of the present application. Example 143 discloses that the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8, including primary lung and colon tumors of the type and stage indicated in Table 7. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan™ PCR. Table 8 shows the resulting gene amplification data. Further, Example 143 explains that the results of TaqMan™ PCR are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc.

Appellants respectfully submit that a ΔCt value of at least 1.0 was observed for PRO1293 in at least three of the tumors listed in Table 8. PRO1293 showed approximately 1.71 ΔCt units which corresponds to $2^{1.71}$- fold amplification or 3.272-fold amplification in primary lung tumor (HF-000840), and approximately 1.13-2.33 ΔCt units which corresponds to $2^{1.13}$ -$2^{2.33}$- fold amplification or 2.189 fold to 5.028-fold amplification in colon tumors (HF-000539 and HF-000795). (See Table 8 and page 507, lines 5-12 of the specification). Accordingly, the present specification clearly discloses overwhelming evidence that the gene encoding the PRO1293 polypeptide is significantly amplified in lung and colon tumors.

It is also well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Appellants have submitted, in their Response filed September 9, 2004, a Declaration by Dr. Audrey Goddard. Appellants particularly draw the Board's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

As indicated above, the gene encoding the PRO1293 polypeptide shows at least a two fold amplification in three different lung and colon tumors. In addition, the Goddard Declaration clearly establishes that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1293 is a diagnostic marker of lung and colon cancer.

The Examiner has asserted that "[t]he asserted utilities of cancer diagnostics for the claimed antibody that binds to the polypeptide of SEQ ID NO:77, are credible and specific. However, they are not substantial. The data set forth in the specification are preliminary at best." (Pages 5-6 of the Office Action mailed November 29, 2004).

As stated above, in explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement[18] states, "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

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[18] M.P.E.P. §2107 II (B)(1).

Appellants' position is based on the overwhelming evidence from gene amplification data disclosed in the specification which clearly indicate that the gene encoding PRO1293 is significantly amplified in certain lung and colon tumors. Based on the working hypothesis among those skilled in the art that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, one skilled in the art would simply accept that since the PRO1293 gene is amplified, the PRO1293 polypeptide would be more likely than not over-expressed. Thus data relating to PRO1293 polypeptide expression may be used for the same diagnostic and prognostic purposes as data relating to PRO1293 gene expression. Therefore, based on the disclosure in the specification, no further research would be necessary to determine how to use the claimed PRO1293 polypeptides, because the current invention is fully enabled by the disclosure of the present application.

Accordingly, Appellants submit that based on the general knowledge in the art at the time the invention was made and the teachings in the specification, the specification provides clear guidance as to how to interpret and use the data relating to the PRO1293 polypeptide expression and that the PRO1293 polypeptides have utility in the diagnosis of cancer.

C. A *prima facie* case of lack of utility has not been established

The Examiner has asserted that the "the instant specification does not demonstrate that the increased copy number of PRO1293 DNA in lung and colon tumors, leads to an increased expression of PRO1293 polypeptide in these tumors." (Page 4 of the Office Action mailed November 29, 2004). The Examiner concludes that "since Applicants do not provide information regarding the level of expression, an activity, or a role in cancer or any other disease for the claimed PRO1293 polypeptide, the polypeptide lacks a substantial activity or well established utility." (Page 5 of the Office Action mailed November 29, 2004).

The Examiner has cited Pennica *et al.* in support of the assertion that "protein levels cannot be accurately predicted from the level of the corresponding gene." (Page 5 of the Office Action mailed May 13, 2004). The Examiner has further cited Hu *et al.*, in support of the assertion that "the literature reports that gene amplification does not *necessarily* result in increased expression at the mRNA and polypeptide levels." (Page 5 of the Office Action mailed November 29, 2004; emphasis added).

As a preliminary matter, Appellants respectfully submit that it is not a legal requirement to establish that gene amplification "necessarily" results in increased expression at the mRNA and polypeptide levels, or that protein levels can be "accurately predicted." As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Appellants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Appellants submit that Pennica *et al.* does not show a lack of correlation between gene (DNA) amplification and mRNA levels. According to the quoted statement from Pennica *et al.*, "WISP-1 gene amplification in human colon tumors showed a correlation between DNA amplification and over-expression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased polypeptide expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression

in human colon tumors *showed a correlation between DNA amplification and over-expression . . . .*" (Pennica *et al.*, page14722, left column, first full paragraph, emphasis added).

Accordingly, Appellants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-expression of the encoded WISP polypeptide. More importantly, the teaching of Pennica *et al.* is specific to *WISP* genes. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression in general.

The Examiner futher cites Hu *et al.* to the effect that genes displaying a 5-fold change or less in mRNA expression in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease.

Appellants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Accordingly, contrary to the Examiner's assertion, Appellants submit that Hu *et al.* does not conclusively show that it is more likely than not that gene amplification does not result in increased expression at the mRNA and polypeptide levels. First, the title of Hu *et al.* is "Analysis of Genomic and Proteomic Data Using Advanced Literature Mining." As the title clearly suggests, the conclusion suggested by Hu *et al.* is merely based on a statistical analysis of the information disclosed in the published literature. As Hu *et al.* states, "We have utilized a computational approach to literature mining to produce a comprehensive set of gene-disease relationships." In particular, Hu *et al.* relied on the MedGene Database and the Medical Subject Heading (MeSH) files to analyze the gene-disease relationship. More specifically, Hu *et al.* "compared the MedGene breast cancer gene list to a gene expression data set generated from a micro-array analysis comparing breast cancer and normal breast tissue samples." (See page 408, right column).

Therefore, Applicants first submit that the reference by Hu *et al.* only studies the statistical analysis of micro-array data and not gene amplification data. Therefore, their findings would not be directly applicable to gene amplification data. In addition, Applicants respectfully

submit that the Hu *et al.* reference does not show that a lack of correlation between microarray data and the biological significance of cancer genes is typical.

According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Applicants further submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation reflects only the current research interest of a molecule rather than the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in scientific study that important molecules are overlooked by the scientific society for many years until the discovery of their true function. Therefore, Appellants submit that Hu *et al.* drew their conclusion based on a very unreliable standard and that their research does not provide any meaningful information regarding the correlation between microarray data and the biological significance of a molecule.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and can not be generalized as a principle governing microarray study of

breast cancer in general, let alone the various other types of cancer genes in general. In fact, even Hu *et al* admit that., "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added).

In summary, Applicants respectfully submit that the Examiner has not shown that a lack of correlation between microarray data and the biological significance of cancer genes, as observed for ER-positive breast tumor, is typical. Since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance. The Patent Office has failed to meet its initial burden of proof that Appellants' claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the Pennica *et al.* and Hu *et al.* articles do not provide sufficient reasons to doubt the statements by Appellants that PRO1293 has utility. As discussed above, the law does not require that gene amplification "necessarily" results in increased expression at the mRNA and polypeptide levels, or that protein levels must be "accurately predicted." Therefore, Appellants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited references and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

D. It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Appellants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Appellants' Response filed October 25, 2004) collectively teach that in general, gene amplification increases mRNA expression. Second, the Declaration of Dr. Paul Polakis,

principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels. Thus, taken together, all of the submitted evidence supports Applicants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

Appellants submit that there are numerous articles which show that generally, if a gene is amplified in cancer, it is more likely than not that the mRNA transcript will be expressed at an elevated level. For example, Ornfoft *et al.* (*Mol. and Cell. Proteomics*, 2002, vol. 1, pages 37-45 - made of record in Appellants' Response filed September 9, 2004) studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material using an array-based method. Ornfoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (*Cancer Res.*, 2002, vol. 62, pages 6240-45 - made of record in Appellants' Response filed September 9, 2004) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (See page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (*PNAS*, 2002, vol. 99, pages 12963-12968 - made of record in Appellants' Response filed September 9, 2004) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

In addition, in their Response filed September 9, 2004, Appellants submitted a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with

protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To the date of the Declaration, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested according to the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (i.e., that it is more likely than not informative of the protein level).

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and

mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1293 gene, that the PRO1293 polypeptide is concomitantly overexpressed. Accordingly, Applicants submit that the PRO1293 polypeptides and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the claimed polypeptides for diagnosis of cancer.

In the Office Action mailed November 29, 2004, the Examiner asserted that "Orntoft *et al.* do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time.... Orntoft *et al.* concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p.40). This analysis was not done for PRO1293 in the instant specification. That is, it is not clear whether or not PRO1293 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Orntoft *et al.* is not clear." (Page 8 of the Office Action mailed November 29, 2004). The Examiner further alleges, "Hyman *et al.* used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract).... Therefore, Hyman *et al.* also do not support utility of the polypeptides of the instant invention." (Page 8 of the Office Action mailed November 29, 2004). The Examiner further alleges that "Pollack *et al* also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack *et al.* did not investigate polypeptide levels." (Pages 8-9 of the Office Action mailed November 29, 2004).

Appellants respectfully point out that in Orntoft *et al.*, 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by hybridizing tumor DNA to normal metaphase chromosomes (CGH). Orntoft *et al.* used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas.

Orntoft *et al* found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a cluster of genes having increased mRNA expression (see page 40). Orntoft *et al.* state, "For both tumors TCC733 ($p<0.015$) and TCC827 ($p<0.00003$) a highly significant correlation was observed between the level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (see page 41, column 1). Orntoft *et al.*, also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis. Orntoft *et al.* state, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Orntoft *et al.* clearly support Appellants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

The Examiner has stated that Appellants have not indicated whether PRO1293 is in a gene cluster region of a chromosome. (Page 8 of the Office Action mailed November 29, 2004). Appellants fail to see how this is relevant to the analysis. Orntoft *et al.* did not limit their findings to only those regions of amplified gene clusters. Further, as discussed below, Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes.

Appellants respectfully submit that the Examiner has mischaracterized the methods used by Hyman *et al.* and Pollack *et al* in their analysis. These papers did not use traditional CGH analysis to identify amplified genes. In Hyman *et al.*, 13,824 cDNA clones were placed on glass slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs was hybridized to the cDNA sequences. For expression analysis, RNA from tumor cell lines was hybridized on the same microarrays. The 13,824 arrayed cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman *et al.* state, "The results illustrate a considerable influence of copy number on gene expression patterns." For example, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e.*, belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, column 1). Further, Hyman *et al.* state that "[t]he cDNA/CGH microarray technique enables the direct correlation of copy number

and expression data on a gene-by-gene basis throughout the genome." (See page 6242, column 2). Therefore, the analysis performed by Hyman *et al.* was on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack *et al.*, DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

The Examiner further asserts that "none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics" (Page 9 of the Office Action mailed November 29, 2004). Appellants respectfully point out that Hyman *et al.* conducted additional studies of one of the genes found to be amplified, HOXB7, and found "a clinical association between HOXB7 amplification and poor patient prognosis." (Page 6244, col.1 to col.2). Thus the results of Hyman *et al.* confirm that genes which are amplified in tumors have prognostic utility. The Board's attention is also respectfully directed to the final paragraph of Pollack *et al.*, wherein the authors conclude that "a substantial portion of the phenotypic uniqueness (and, by extension, the heterogeneity in clinical behavior) among patients' tumors may be traceable to underlying variation in DNA copy number." (Page 12698, col. 2). Accordingly, Pollack *et al.* confirm that genes that are amplified in at least one type of tumor are useful as markers for that type of tumor.

With regard to the correlation between mRNA expression and protein levels, the Examiner has asserted that the Polakis Declaration is insufficient to overcome the rejection of claims 28-36 and 38-40 since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels and not gene amplification levels. The Examiner further asserted that the declaration does not provide data such that the Examiner can independently draw conclusions. (Page 10 of the Office Action mailed November 29, 2004).

Appellants submit that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels, the correlation between gene amplification and mRNA levels having already been established by the data shown in the Orntoft *et al.,* Hyman *et al.,* and Pollack *et al.* articles. Appellants emphasize that the opinions expressed in the Polakis Declaration, including the quoted statement, are all based on factual findings. Thus, Dr. Polakis explains that in the course of their research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[19] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a

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[19] *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

preponderance of the evidence with due consideration to persuasiveness of argument"[20] Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner"[21]. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[22] which states, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Polakis Declaration) states that "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." Therefore, barring evidence to the contrary regarding the above statement in the Polakis Declaration, this rejection is improper under both the case law and the Utility guidelines.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1293 gene, that the PRO1293 polypeptide is concomitantly overexpressed. Thus, Appellants submit that the claimed PRO1293 polypeptides have utility in the diagnosis of cancer.

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[20] *In re Alton,* 37 USPQ2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)).

[21] *In re Alton, supra.*

[22] Part IIB, 66 Fed. Reg. 1098 (2001).

E. Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which Appellants submit is **not** true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a specific, substantial, and credible utility. In support, Appellants respectfully draw the Board's attention to page 2 of the Declaration of Dr. Avi Ashkenazi (submitted with the Response filed September 9, 2004) which explains that,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Appellants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also has the benefit that the patient can avoid exposure to the side effects associated with such agents.

This utility is further supported by the teachings of the article by Hanna and Mornin. (Pathology Associates Medical Laboratories, August (1999); submitted with the Response filed September 9, 2004). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinomas. Further, the article teaches that diagnosis of breast cancer includes

testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Examiner has asserted that "Hanna et al. supports the rejection, in that Hanna et al. show that gene amplification does not reliably correlate with protein over-expression, and thus the level of polypeptide expression must be tested empirically." (Page 7 of the Office Action mailed November 29, 2004). Appellants respectfully point out that the Examiner appears to have misread Hanna *et al.* Hanna *et al.* clearly state that gene amplification (as measured by FISH) and polypeptide expression (as measured by immunohistochemistry, IHC) are well correlated ("in general, FISH and IHC results correlate well" (Hanna *et al.* p. 1, col. 2)). It is only a subset of tumors which show discordant results. Thus Hanna *et al.* support Appellants' position that it is more likely than not that gene amplification correlates with increased polypeptide expression.

Appellants have clearly shown that the gene encoding the PRO1293 polypeptide is amplified in at least three lung and colon tumors. Therefore, the PRO1293 gene, similar to the HER-2/neu gene disclosed in Hanna *et al.*, is a tumor associated gene. Furthermore, as discussed above, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1293 gene, that the PRO1293 polypeptide is concomitantly overexpressed.

However, even if gene amplification does not result in overexpression of the gene product (*i.e.*, the protein) an analysis of the expression of the protein is useful in determining the course of treatment, as supported by the Ashkenazi Declaration and the Hanna paper. The Examiner "agrees that evidence regarding lack of over-expression would be useful" but asserts that "there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not in the instant invention" and that "[f]urther research is required to determine such." (Page 7 of the Office Action mailed November 29, 2004). The Examiner appears to view the testing described in the Ashkenazi Declaration and the Hanna paper as experiments involving further characterization of the PRO1293 polypeptide itself. In fact, such testing is for the purpose of

characterizing not the PRO1293 polypeptide, but the tumors in which the gene encoding PRO1293 is amplified. The PRO1293 polypeptide is therefore useful in tumor categorization, the results of which become an important tool in the hands of a physician enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient.

For the reasons given above, Appellants respectfully submit that the present specification clearly describes, details and provides a patentable utility for the claimed invention. Accordingly, Appellants respectfully request reconsideration and reversal of the rejections of Claims 28-36 and 38-40 under 35 U.S.C. §101.

ISSUE II: Claims 28-36 and 38-40 satisfy the enablement requirement of 35 USC §112, first paragraph.

Claims 28-36 and 38-40 stand rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Page 4 of the Office Action mailed November 29, 2004).

In this regard, Appellants refer to the arguments and information presented above in response to the outstanding rejection under 35 U.S.C. § 101, wherein those arguments are incorporated by reference herein. Appellants respectfully submit that as described above, the PRO1293 polypeptides have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the claimed polypeptides for diagnosis of cancer, without undue experimentation.

The Examiner has further asserted that even if Applicants established an activity for the polypeptide of SEQ ID NO:77,

> Due to the large quantity of experimentation necessary to determine all the polypeptides comprising an amino acid that is at least 80%, 85%, 90%, 95% or 99% identical to the polypeptide of SEQ ID NO:77, and to screen an activity for them, the lack of direction/guidance presented in the specification regarding which variants of the polypeptide of SEQ ID NO:77 would retain the desired activity. . . the unpredictability of the effects of mutation on the structure and function of the claimed polypeptide, and the breadth of the claims which fail to recite particular biological activities, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. (Pages 11-12 of the Office Action mailed November 29, 2004).

Appellants note that the claimed variants all share the functional limitation that "the nucleic acid encoding said polypeptide is amplified in lung or colon tumors." Thus the claims recite "particular biological activities" as required in the Office Action. Appellants note that since the recited activity is that of the encoding nucleic acids, consideration of "the effects of mutation on the structure and function of the claimed polypeptide" are not relevant. As discussed above, under Issue I concerning the rejection under 35 U.S.C. § 101, polypeptides wherein the encoding nucleic acid is amplified in tumor tissue are themselves more likely than not to be over-expressed in tumor tissues; thus they have utility as markers for those tumor types in which they are over-expressed. Further, as discussed above, under Issue I concerning the rejection under 35 U.S.C. § 101, simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor. Accordingly, one of ordinary skill in the art would understand how to use polypeptide variants wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors in the diagnosis or classification of cancer.

Example 143 of the present application provides step-by-step guidelines and protocols for the gene amplification assay. By following the disclosure in the specification, one skilled in the art can easily test whether a gene encoding a variant PRO1293 protein is amplified in lung or colon tumors. The specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 302, line 4, to page 305, line 4). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 354, line 30 to page 357, line 7). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 356). Accordingly, one of skill in the art could identify whether the variant PRO1293 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 354, line 30

to page 358, line 34) and methods of preparing the PRO polypeptides (see page 358, line 35 and onward).

Therefore, Appellants respectfully submit that the specification provides ample guidance such that one of skill in the art could readily test a nucleic acid sequence which encodes a variant polypeptide to determine whether it is amplified by the methods set forth in Example 143. Furthermore, one of ordinary skill in the art has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO:77. Accordingly, one of ordinary skill could practice the claimed invention without undue experimentation.

The claims currently recite polypeptide sequences associated with a biological activity of the encoding polynucleotides. This biological activity together with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that, one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed polypeptide sequences without undue experimentation. As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."[23]

As discussed above, a considerable amount of experimentation is permissible, if it is merely routine. Applicants submit that the identification of variant PRO1293 polypeptides having at least 80% identity to SEQ ID NO:77 wherein the polynucleotide encoding the polypeptide is amplified in lung or colon tumors, can be performed by techniques that were well known in the art at the priority date of this application, and that the performance of such work does not require undue experimentation.

Accordingly, Appellants respectfully request reconsideration and reversal of the enablement rejection of Claims 28-36 and 38-40 under 35 U.S.C. §112, first paragraph.

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[23] M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers,* 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

ISSUE III: Claims 28-32 satisfy the written description requirement of 35 U.S.C. §112, First Paragraph

Claims 28-32 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking adequate written description. In particular, the Examiner has asserted that "[a]lthough the specification describes the structure of PRO1293 polypeptide, the skilled artisan would not be able to visualize the structure of the polypeptides having at least at least 80%, 85%, 90%, 95% or 99% identity with the polypeptide of SEQ ID NO:77, because the claims are not described by structure and functional identity." (Page 12 of the Office Action mailed November 29, 2004).

Currently pending Claims 28-32 recite the functional limitation that the nucleic acid encoding the polypeptide is amplified in lung or colon tumors. Accordingly, coupled with the general knowledge available in the art at the time of the invention, Appellants submit that the specification provides ample written support for the claimed polypeptides in Example 143, where methods of detecting and quantifying amplification in several tumors and/or cell lines are described. Thus, based on the high percentage of sequence identity and the described method of detecting and quantifying amplification in tumors, one skilled in the art would have known at the time of the invention that the Appellants had possession of the claimed polypeptides.

A. The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[24] [25] The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[26] The factual determination in a

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[24] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[25] *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

[26] *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. [27] [28]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[29] , the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).[30] Further, The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[31] [32]

B. The Disclosure Provides Sufficient Written Description for the Claimed Invention

Appellants respectfully submit that the instant specification evidences the actual reduction to practice of the amino acid sequence of SEQ ID NO:77. TheExaminer has acknowledged that polypeptides comprising the sequence set forth in SEQ ID NO:77 meet the written description provision of 35 U.S.C. §112, first paragraph. (Page 12 of the Office Action mailed November 29, 2004). Thus, the genus of polypeptides with at least 80% sequence identity to SEQ ID NO:77, which possess the functional property of having a nucleic acid which is amplified in lung or colon tumors would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

Appellants have provided native PRO sequence SEQ ID NO:77. The present application also describes methods for identifying genes which are amplified in lung or colon tumors.

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[27] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[28] *See also* M.P.E.P. §2163 II(A).

[29] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

[30] *See also* M.P.E.P. §2141.03.

[31] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[32] See *also* M.P.E.P. §2141.03.

Example 143 of the present application provides step-by-step guidelines and protocols for the gene amplification assay. By following the disclosure in the specification, one skilled in the art can easily test whether a gene encoding a variant PRO1293 protein is amplified in lung or colon or tumors. The specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 302, line 4 to page 305, line 4). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 354, line 30 to page 357, line 7). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 356). Accordingly, one of skill in the art could identify whether the variant PRO1293 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specification sets forth methods for making the amino acid sequences (see page 354, line 30 to page 358, line 34) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward).

Therefore, Appellants respectfully submit that one of skill in the art could readily test a nucleic acid sequence which encodes a variant polypeptide to determine whether it is amplified by the methods set forth in Example 143.

The Examiner has asserted that "although the claims recite both percent identity and functional language, the recited function is for the nucleic acid encoding the polypeptide of SEQ ID NO:77, and not for the polypeptide itself. The specification does not disclose a function for the polypeptide of SEQ ID NO:77, neither does the specification disclose a variant of the polypeptide of SEQ ID NO:77 that displays an activity." (Page 12 of the Office Action mailed November 29, 2004). In this regard, Appellants refer to the arguments and information presented above in response to the outstanding rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, for alleged lack of utility and enablement. These arguments are incorporated by reference herein. Appellants respectfully submit that as discussed above under Issue I, the teachings in the art, as exemplified by Ornoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the

mRNA and protein levels. Thus the amplification of the encoding polynucleotide in tumors does provide useful information regarding the functional property of the polypeptide in being overexpressed in tumor tissues.

Appellants further respectfully submit that whether or not the polypeptide is also overexpressed in tumor tissues is irrelevant to the consideration of adequate written description. The claims have characterized the recited polypeptides as having the property that their encoding polynucleotides are amplified in lung or colon tumors. As discussed above, the specification describes methods for identifying genes which are amplified in lung or colon tumors. Therefore, one of skill in the art could readily test a nucleic acid sequence which encodes a variant polypeptide to determine whether it is amplified by the methods set forth in Example 143. Thus, the recited property of amplification of the encoding gene adds to the characterization of the claimed polypeptide sequences in a manner that one of skill in the art could readily assess and understand.

As discussed above, Appellants have recited structural features, namely, 80% sequence identity to SEQ ID NO:77, which are common to the genus. Appellants have also provided guidance as to how to make the recited variants of SEQ ID NO:77, including listings of exemplary and preferred sequence substitutions. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids. Accordingly, a description of the claimed genus has been achieved.

For the above reasons, the specification provides adequate written description for polypeptides having at least 80% identity to SEQ ID NO:77 wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors. Accordingly, Appellants respectfully request reconsideration and reversal of the written description rejection of Claims 28-32 under 35 U.S.C. §112, first paragraph.

ISSUE IV: Claims 28-36 and 38-40 are not anticipated under 35 U.S.C. §102(a) by Botstein *et al.*, WO 2000053751 or Baker *et al.*, WO 200012708.

Claims 28-36 and 38-40 stand rejected under 35 U.S.C. §102(a) as being anticipated by Botstein *et al.*, WO200053751, published on September 14, 2000, and by Baker *et al.*, WO200012708, published on March 9, 2000.

Appellants submit that, as discussed above in response to the outstanding rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, for alleged lack of utility and enablement (Issue I and Issue II), Appellants rely on the gene amplification results (Example 143) to establish a credible, substantial and specific asserted utility for the polypeptide PRO1293. These results were first disclosed in U.S. Provisional Application Serial No. 60/162,506, filed on October 29, 1999. As discussed above, the disclosure of the instant application, which is similar to that of the earlier-filed application (U.S. Provisional Application Serial No. 60/162,506), provides the support required under 35 U.S.C. §112 for the subject matter of the instant claims. Accordingly, Applicants submit that the subject matter of the instant claims is disclosed in the manner provided by 35 U.S.C. §112 in U.S. Provisional Application Serial No. 60/162,506. Therefore, the effective filing date of this application is October 29, 1999, the filing date of U.S. Provisional Application Serial No. 60/162,506.

The PCT patent application by Botstein *et al.*, WO200053751, was published on September 14, 2000, which is over ten months after the effective filing date of the instant application; hence Botstein *et al.* is not prior art.

The PCT patent application by Baker *et al.*, WO200012708, was published on March 9, 2000, which is over four months after the effective filing date of the instant application; hence Baker *et al.* is not prior art.

The Examiner has asserted that the subject matter of the claimed invention "is not supported by the disclosure in...60/162,506, filed October 29, 1999, since the prior application does not provide a specific and substantial utility or a well established utility for the claimed invention." The Examiner has further asserted that "the increased copy number of PRO1293 DNA in said tumors, does not provide a readily apparent use for the polypeptide of SEQ ID NO:77, because the assay does not show that the polypeptide is also amplified in these tumors." (Pages 2-3 of the Office Action mailed November 29, 2004).

In this regard, Appellants refer to the arguments and information presented above in response to the outstanding rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, for alleged lack of utility and enablement. These arguments are incorporated by reference herein. Appellants respectfully submit that as described above under Issue I, the presently claimed

invention is supported by a specific, substantial and credible utility and, therefore, the present specification teaches one of ordinary skill in the art "how to use" the claimed invention without undue experimentation, as described above.

Accordingly, Appellants respectfully request reconsideration and reversal of the rejection of Claims 28-36 and 38-40 under 35 U.S.C. §102(b) as being anticipated by Botstein *et al.* or Baker *et al.*

9. CONCLUSION

For the reasons given above, Appellants submit that the specification discloses at least one patentable utility for the PRO1293 polypeptides of Claims 28-36 and 38-40, and that one of ordinary skill in the art would understand how to used the claimed polypeptides, for example in the diagnosis of lung and colon tumors. Therefore, claims 28-36 and 38-40 meet the requirements of 35 USC §101 and 35 USC §112, first paragraph. Further, this patentable utility for the claimed polypeptides was first disclosed in U.S. Provisional Application Serial No. 60/162,506, filed on October 29, 1999, priority to which is claimed in the instant application. Accordingly, the instant application has an effective priority date of October 29, 1999, and therefore Botstein *et al.*, WO200053751, published on September 14, 2000, and Baker *et al.*, WO200012708, published on March 9, 2000, are not prior art and do not anticipate the claims under 35 USC §102(a).

Appellants further submit that the recited polypeptide variants of claims 28-32 meet the written description requirement of 35 USC §112, first paragraph.

Accordingly, reversal of all the rejections of claims 28-36 and 38-40 is respectfully requested.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C3**).

Respectfully submitted,

Date: July 27, 2005

By: _____
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APPENDIX A

Claims on Appeal

28. An isolated polypeptide having at least 80% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:77;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:77, lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:77; or

(d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203292;

wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors.

29. The isolated polypeptide of Claim 28 having at least 85% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:77;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:77, lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:77; or

(d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203292;

wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors.

30. The isolated polypeptide of Claim 28 having at least 90% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:77;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:77, lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:77; or

(d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203292;

wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors.

31. The isolated polypeptide of Claim 28 having at least 95% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:77;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:77, lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:77; or

(d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203292;

wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors.

32. The isolated polypeptide of Claim 28 having at least 99% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:77;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:77, lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:77; or

(d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203292;

wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors.

33. An isolated polypeptide comprising:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:77;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:77, lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:77; or

(d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203292.

34. The isolated polypeptide of Claim 33 comprising the amino acid sequence of the polypeptide of SEQ ID NO:77.

35. The isolated polypeptide of Claim 33 comprising the amino acid sequence of the polypeptide of SEQ ID NO:77, lacking its associated signal peptide.

36. The isolated polypeptide of Claim 33 comprising the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:77.

38. The isolated polypeptide of Claim 33 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203292.

39. A chimeric polypeptide comprising a polypeptide according to Claim 28 fused to a heterologous polypeptide.

40. The chimeric polypeptide of Claim 39, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin.